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APPLICATION NO.	FILING DATE	FIRST NAME/INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/673,786	09/30/2003	Valery Zavenovich Akhverdian	US-115	7880

38108 7590 05/11/2007
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EXAMINER

RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
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1652

MAIL DATE	DELIVERY MODE
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05/11/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/673,786	Applicant(s) AKHVERDIAN ET AL.	
	Examiner Delia M. Ramirez	Art Unit 1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 18 April 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
 b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(i).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
 (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
 (b) ☐ They raise the issue of new matter (see NOTE below);
 (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
 (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
 5. ☒ Applicant's reply has overcome the following rejection(s): see attached.
 6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
 7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
 The status of the claim(s) is (or will be) as follows:
 Claim(s) allowed: none.
 Claim(s) objected to: _____.
 Claim(s) rejected: 12, 15, 16, 19 and 23.
 Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
 9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
 10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
 12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
 13. ☐ Other: _____.

ADVISORY ACTION

1. Claims 12, 15-16, 19, 23 are pending.
2. The request for entering amendments to claims 12, 23, cancellation of claims 21-22, 24, and arguments filed on 4/18/2007 under 37 CFR 1.116 in reply to the Final Action mailed on 1/18/2007 are acknowledged. The proposed amendments to the claims will be entered. While the amendments to the claims seem to overcome the previously applied 35 USC 112, first paragraph rejections, the claims as amended still remain rejected under 35 USC 103(a) for the reasons of record. Also, it is noted that amended claim 12 would be objected to due to a typographical error. The terms "copy number of said gene" should be replaced with "copy number of said genes" and the term "placing said gene" should be replaced with "placing said genes".
3. Applicant traverses the 35 USC 103(a) rejection on the grounds that (1) it would not have been expected that an additional increase in threonine production would result by increasing the expression of the gene encoding the protein of SEQ ID NO: 2 because threonine production is already increased in a cell with increased expression of the thrA, thrB, thrC, and rhtA genes, and (2) one of skill in the art would not have known which reaction is the rate limiting step in threonine synthesis or whether the synthesis reaction of aspartic acid from oxaloacetate is the rate limiting step. Therefore, Applicant submits that an increase in threonine production by increasing the expression of the aspC, thrA, thrB, thrC, and rhtA genes in *E. coli* is completely unexpected, novel and non-obvious.
4. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. There is no evidence in the specification or the art that the maximum amount of L-threonine that can be produced in *E. coli* is that obtained from an *E. coli* which has increased expression of the thrA, thrB, thrC, and rhtA genes. There is no indication that the increased expression of these genes would preclude additional synthesis of L-threonine if an additional modification is made to an *E. coli* cell that already is able to overexpress the thrA, thrB, thrC, and rhtA genes. Thus, unless there is a

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teaching or suggestion that additional modifications aimed at increasing the availability of precursors of threonine would either have no effect or impair the synthesis of threonine, one of skill in the art would conclude that there is a reasonable expectation that increasing the amount of a precursor of L-threonine would result in additional synthesis of L-threonine. The Examiner acknowledges that a "bottleneck" may exist in the *E. coli* strain of Debabov et al. which would not allow an increase in L-threonine even if the synthesis of aspartic acid increases. However, there is no teaching suggesting that such bottleneck exists in the *E. coli* strain of Debabov et al. or that increasing the expression of the aspC gene in the *E. coli* strain of Debabov et al. would not allow additional increase in L-threonine production.

The argument that the lack of knowledge as to which was the rate limiting step in the synthesis of L-threonine from aspartic acid at the time the invention was made makes the results obtained unexpected and the claimed invention non-obvious is not persuasive. Even without this knowledge, the teachings of the art clearly provide one of skill in the art motivation to combine the references cited and a reasonable expectation of success. Assuming, arguendo, that the rate limiting step in the production of L-threonine is the conversion of oxaloacetate to aspartic acid, and this knowledge would have been available to one of skill in the art at the time the invention was made, it is noted that such knowledge would have only provided a greater motivation to combine the references cited, and a greater expectation of success at obtaining an increase in L-threonine production. The art, as evidenced by the specification on page 3, paragraph [10], teaches that a similar approach (increased expression of the aspC gene) was followed in the production of L-lysine in *E. coli*, which is also synthesized from aspartic acid, that resulted in increased production of L-lysine. Also, Katsumata et al. clearly teaches the increased production of L-threonine by increasing the expression of the aspC gene in *C. glutamicum*. Therefore, while there is no absolute certainty that an increase in L-threonine production could be achieved by increasing the expression of the *E. coli* aspC gene taught by Edwards et al. in the *E. coli* strain of Debabov et al., it is clear from the art that there is not only motivation but a reasonable expectation of success at increasing

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production of L-threonine by increasing the expression of the aspC gene. Therefore, for the reasons of record and those set forth above, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

5. For purposes of Appeal, the status of the claims is as follows:

Claim(s) allowed: NONE

Claims(s) objected to:

Claim(s) rejected: 12, 15-16, 19, 23

Claim(s) withdrawn from consideration: NONE

6. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



Delia M. Ramirez, Ph.D.
Primary Patent Examiner
Art Unit 1652

DR
May 1, 2007